REMARKS

By the foregoing amendments, Claims 44-47 have been cancelled, Claims 48-68 have been amended, and new Claims 69-111 have been added. The foregoing amendments are believed to place the claims submitted herewith in condition for allowance, as further discussed below.

Applicants' attorneys (Ralph Selitto, Jr. and Eric Bleich) thank Examiner Singh and Examiner Saucier for the personal interview conducted on August 18, 2009 at the United States Patent and Trademark Office. During the interview, the Examiners and applicants' attorneys discussed the prior art rejections contained in the Office Action, which rejections were based on one primary reference (i.e., U.S. Patent No. 5,782,835 to Hart et al. ("the Hart et al. Patent")) and three secondary references (i.e., U.S. Patent No 6,267,786 to Stone ("the Stone Patent"), an article by Peretti et al. ("the Peretti Article"), and an article by Hoffman ("the Hoffman Article")). As indicated in the Interview Summary dated August 18, 2009, the Examiners and applicants' attorneys also discussed a draft independent claim, and the differences between the combination recited therein and the apparatus and methods disclosed in the Hart et al. Patent. While no agreement was reached regarding the allowability of the draft claim, the Examiners proposed various revisions. In writing the new independent claims submitted herewith, applicants' attorneys have taken into account the comments and revisions that emanated from the aforesaid Examiner interview.

By way of background, known articular cartilage repair procedures involve the use of an implant formed from osteochondral tissue that is harvested from a donor. The implant is known as an "autograft" when the donor is also the patient (i.e., the recipient of

the implant). On the other hand, the implant is known as an "allograft" when the donor is another individual of the same species as the patient. One issue concerning the use of allografts is the potentially adverse immunological response upon implantation in a patient, and the subsequent rejection of the allograft. Another issue is the availability of implants formed from osteochondral tissue for surgical procedures, especially in cases where the surgeon considers the use of an autograft to be undesirable or impossible. Yet another issue in the use of osteochondral tissue implants is the efficiency, quality and speed of cellular migration and tissue integration between the implant and the patient's surrounding tissue.

The foregoing issues are addressed by the combinations that are disclosed and claimed in the present application. More particularly, the allograft osteochondral plugs recited in new independent Claims 69 and 84 are **decellularized**, thereby eliminating the risk of an adverse immunological response. Once decellularized, the allograft osteochondral plug may be stored for future use, allowing a surgeon to order the plugs in advance of a surgical repair procedure. Decellularization of the osteochondral plug is also believed to provide signals that stimulate chondrocytes and other cells in a patient's surrounding cartilage tissue to migrate into the osteochondral plug to proliferate therein, thereby enhancing integration of the osteochondral plug with the patient's surrounding cartilage tissue. Decellularization of the osteochondral plug also increases its porosity, which facilitates the entry of a greater number of cells from the patient's surrounding cartilage tissue into the osteochondral plug. Because the osteochondral plug is decellularized, it is depleted of chondrocytes, which necessitates the addition of the cartilage mixture. Combining the cartilage mixture with the osteochondral plug further

promotes and enhances the integration of the osteochondral plug with the patient's surrounding cartilage tissue.

New independent Claim 69 recites a combination for repairing an articular cartilage defect. The combination includes a decellularized allograft osteochondral plug, and a quantity of cartilage mixture. The decellularized allograft osteochondral plug has a decellularized subchondral bone base and a decellularized cartilage cap. The cartilage mixture contains milled allograft cartilage pieces mixed in a biocompatible carrier.

While Claim 69 is a combination claim, it also includes a product-by-process recitation in connection with the decellularized allograft osteochondral plug. Specifically, the osteochondral plug is formed by first harvesting a **non-decellularized** osteochondral plug from a human donor, and then **treating** the non-decellularized osteochondral plug to **remove** cellular material, chondrocytes, pluripotent mesenchymal cells and proteoglycans therefrom. The osteochondral plug is adapted for insertion into a bore formed in a cartilage defect area of the patient such that the decellularized cartilage cap is spaced from a cartilage layer of the patient, while the decellularized subchondral bone base is spaced from an adjacent bone layer of the patient. As a result, an annular space is formed having a size sufficient to contain a quantity of cartilage mixture. Because the annular space extends along substantially the entire length of the osteochondral plug, the quantity of cartilage mixture is sufficient for promoting chondrocyte migration into and proliferation within the decellularized cartilage cap, while enhancing tissue integration between the decellularized subchondral bone base and the patient's adjacent tissue.

In view of the submission of new independent Claims 69 and 84, the rejected independent claim (i.e., Claim 44) has been cancelled, along with dependent Claims 45-47.

The remaining rejected dependent claims (i.e., Claims 48-68) have been amended to depend from new Claim 69. In the foregoing circumstances, applicants' attorneys respectfully submit that the prior art rejections of Claims 44-68 are now rendered moot. However, to facilitate Examiner Singh's consideration of this Amendment, applicants' attorneys are including the following discussion of the distinctions between the inventions recited in new independent Claims 69 and 84 and the cited prior art references. More particularly, applicants' attorneys reiterate herein their position that the Hart et al. Patent (i.e., the primary reference), whether considered alone or in legitimate combination with the Stone Patent, the Peretti Article, and/or the Hoffman Article (i.e., the secondary references), does not anticipate or render obvious the inventions recited in new independent Claims 69 and 84. For the reasons discussed in detail below, applicants' attorney respectfully submits that new independent Claims 69 and 84 are patentably distinct from the primary and secondary references and any combinations thereof, and are therefore in condition for allowance.

Examiner Singh indicated that the arguments presented in applicants' Amendment filed on May 13, 2009 were found to be unpersuasive. For instance, the Examiner indicated that the "designations of 'autograft' and 'allograft' signifies the donor-recipient relationship ... and does not impart any structural feature(s)." Applicants' argument that the Hart et al. Patent "teaches away from performing any other treatment and/or processing steps" was also found to be unpersuasive "because the structural features of the product recited in [Claim 44] are fully met and/or made obvious by the combined teachings of the cited prior art references." For the reasons explained below,

applicants respectfully disagree with the position taken by Examiner Singh with respect to the claimed structural features and those disclosed in the Hart et al. Patent.

Setting aside the autograft/allograft distinction, applicants' attorneys note that, regardless of the source of the bone tissue graft, the osteochondral plug recited in new Claims 69 is **structurally different** from the bone plug disclosed in the Hart et al. Patent. More particularly, the bone plug of the Hart et al. Patent is freshly cut and contains its native cells and other biological substances when implanted. As discussed with the Examiners during the personal interview, the Hart et al. Patent discloses that the bone plug comprises "intact bone and intact articular cartilage", wherein "**intact**" is defined as subjecting the bone and articular cartilage to "**minimal physical disturbance** during the removal process" (see Column 3, Lines 23-33 of the Hart et al. Patent). The Hart et al. Patent neither discloses nor suggests that the bone plug undergoes any type of decellularization. In contrast, the osteochondral plug of Claim 69 is **decellularized**, with the cellular material, chondrocytes, pluripotent mesenchymal cells and proteoglycans being removed therefrom, thereby resulting in an osteochondral plug that is **structurally different** from the bone plug of the Hart et al. Patent.

While new Claim 69 has been presented as a combination claim, it contains product-by-process language that emphasizes the treatment steps performed on the osteochondral plug (i.e., decellularization). Decellularizing the osteochondral plug causes it to undergo a **structural** change, whereby its porosity, weight, density and other **structural** characteristics are modified. As a result, the osteochondral plug of Claim 69 has a **different structure** than that of a tissue graft that has not been decellularized, such as that of the Hart et al. Patent. An analogous comparison is the structure of an intact honeycomb

that contains honey in its cavities, and that of a honeycomb from which the honey has been removed. Clearly, the structure of the intact, honey-containing honeycomb differs from that of the emptied honeycomb from which the honey has been removed. This comparison illustrates how the intact bone plug of the Hart et al. Patent is structurally different from the decellularized osteochondral plug recited in new Claim 69.

With continued reference to the Hart et al. Patent, Examiner Singh characterized it as disclosing a cartilage repair implant which has been "dimensioned to fit in a drilled bore in a cartilage defect (in the form of a bone plug having a [frictional] fit within the drilled bone hole....)".[1] Examiner Singh also alleged that the Hart et al. Patent "explicitly suggest[s] the use of various bio-adhesives ... to fill the gap between the plug and the hole in the native tissue..." Applicants' attorneys respectfully submit that the Hart et al. Patent neither discloses nor suggests the presence of such a gap, or space, between the bone plug and the hole. In fact, the Hart et al. Patent teaches that it is "necessary" for the outer diameter of the bone plug to be larger than the diameter of the hole, "for the required interference fit of the bone plug within the drilled bone hole." (see Column 8, Lines 1-20, and Figures 8B, 8C and 8D, which illustrate the interference fit of the bone plug 118 within the hole 120). More particularly, the inside diameter of the bone cutting element of the bone core removal tool, and hence the diameter of the bone plug, is 4.97 mm, which is greater than the 4.82 mm outside diameter of the drill bit that is used to create the hole, and thus of the hole itself (see Column 8, Lines 8-16). Because the interference fit requires the bone plug to have a larger diameter than the hole, there will be no annular gap or space between the bone plug and the hole of the Hart et al. Patent implant. In contrast, new Claim 69

[1] The Office Action appears to contain an error at Page 4, Line 1, whereby the word "functional" was used instead of the word "frictional", as disclosed in the Hart et al. Patent at Column 8, Lines 50-51

recites a combination of the decellularized osteochondral plug and a cartilage mixture that is positionable in an **annular** space adjacent the osteochondral plug. Moreover, as recited in Claim 69, the annular space **extends along substantially the entire length of the osteochondral plug**. In other words, the annular space extends from the decellularized cartilage cap of the osteochondral plug to the subchondral bone base thereof. Such an arrangement is <u>not</u> disclosed in the Hart et al. Patent, and would not be physically possible, given the relative dimensions of the bone plug and the drilled bone hole and the resulting interference fit therebetween, as further discussed below.

With further reference to the Hart et al. Patent, FIG. 8C is reproduced below to facilitate consideration and discussion. FIG. 8C has been modified to illustrate the physical behavior of a bio-adhesive upon the implantation of the bone plug. More particularly, the modified FIG. 8C illustrates what applicants' attorneys believe will happen to a bio-adhesive that is applied to the bone plug of the Hart et al. Patent after the bone plug is inserted into the bone hole formed by the surgeon.

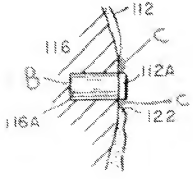

FIG. 8C

As shown at B, a layer consisting of a small portion of the bio-adhesive may be sandwiched between the bottom of the bone portion (116A) of the bone plug and the bottom wall of the drilled bone hole. As also shown at C, the aforementioned interference fit between the bone plug and the bone hole would cause most, if not all, of the remaining portion of the bio-adhesive to be **squeezed out of the bone hole** and towards the cut edges (122) of the patient's surrounding articular cartilage layer (112), adjacent the cartilage surface (112A) of the bone plug. However, as a result of the relative dimensions of the bone plug and the bone hole, as well as the resulting interference fit therebetween, **NO** bio-adhesive could be positioned **along the length of the Hart et al. Patent bone plug that extends between** the bottom of the bone portion (116A) and the cartilage surface (112A) of the bone plug (i.e., between B and C in modified FIG. 8C).

Examiner Singh also indicated that the "adhesive layer" disclosed in the Hart et al. Patent may include "cartilage growth promoting chemical factors". However, unlike the combination recited in new Claim 69, the Hart et al. Patent does **not** disclose the use of a **cartilage mixture** including **milled cartilage pieces** mixed in a **biocompatible carrier**, let alone **milled allograft cartilage pieces**. Even if the Hart et al. Patent did disclose a mixture including cartilage particles, the implanted bone plug would **not** be the same as the combination recited in new Claim 69 because of its lack of an annular space along its **entire length** in which to position the cartilage mixture, as discussed above. In the foregoing circumstances, applicants' attorneys respectfully submit that Hart et al. Patent neither anticipates nor renders obvious the combination recited in new Claim 69.

In addition to the Hart et al. Patent, Examiner Singh cited three secondary references in the Office Action. The secondary references were combined with the Hart et

al. Patent, underscoring Examiner Singh's appreciation of the deficiencies in the Hart et al. Patent that prevented such patent from supporting a rejection of the previously pending claims by itself. For the reasons discussed below, applicants' attorneys respectfully submit that the Hart et al. Patent, even when combined with secondary references, still does not anticipate or make obvious applicants' invention, as recited in Claim 69.

With reference to the Stone Patent, it discloses methods for preparing a soft tissue xenograft for implantation into humans. The preparation includes subjecting the xenograft to cellular disruption treatment and digesting the xenograft with a proteoglycan-depleting factor and/or glycosidase. "Xenograft", as defined in the Stone Patent, refers to a "graft transferred from an animal of one species to one of **another** species." The Stone Patent discusses how a xenograft, when "implanted into an individual, ... provokes immunogenic reactions such as chronic and hyperacute rejection of the xenograft. ... For example, transplantation of soft tissue cartilage xenografts from non-primate animals (i.e., porcine or bovine origin) into humans is primarily prevented by the interaction between the ... antibody present in the serum of humans with the carbohydrate structure ... expressed in the xenograft" (See Col. 4, Lines 23-39). While chronic rejection of a xenograft may occur within one to two weeks of implantation, hyperacute rejection may cause lysis of the vascular bed and stoppage of blood flow in the receiving individual within minutes to two to three hours (See Col. 4, Lines 45-57).

As explained above, the methods disclosed in the Stone Patent are intended to eliminate the adverse **interspecies** biochemical reactions that lead to the rejection of soft tissue xenografts "from a **non-human** animal" when implanted into human recipients. In contrast, new Claim 69 specifically recites an **allograft** osteochondral plug that is harvested

from a **human donor**. The **autograft** bone plug of the Hart et al. Patent is even further removed from the treated xenografts disclosed in the Stone Patent, as a patient would not experience an adverse **interspecies** biochemical reaction to, and rejection of, a tissue graft harvested **from the patient himself**. Thus, in the absence of any risk of such reaction and rejection of the autograft bone plug of the Hart et al. Patent, applicants' attorney respectfully submits that one skilled in the tissue engineering art would **not** be motivated to subject such an autograft bone plug to a method devised for preparing **a xenograft** for implantation into a human patient, as disclosed in the Stone Patent.

As previously noted, the Hart et al. Patent teaches the **immediate** implantation of the **intact** bone plug into **a bone hole drilled** in a patient (See Column 8, Lines 36-48). If the bone plug were subjected to the treatment disclosed in the Stone Patent prior to implantation, the bone plug would no longer be intact, and such implantation could not be immediate. Further, the benefits of using **a freshly cut, viable** autograft bone plug to repair a cartilage defect according to the Hart et al. Patent would be eliminated if such bone plug were subjected to the treatment disclosed in the Stone Patent. In view of the foregoing remarks, applicants' attorneys respectfully submit that the Hart et al. Patent actually **teaches away** from subjecting the bone plug to a treatment, such as that disclosed in the Stone Patent, to remove cellular material, chondrocytes, pluripotent mesenchymal cells and proteoglycans therefrom, as recited in new Claim 69.

In the foregoing circumstances, applicants' attorney respectfully submits that the Hart et al. Patent, the Stone Patent, and the remaining secondary references (i.e., the Peretti et al. article and the Hoffman article), whether considered alone or in combination with each other, fail to anticipate and/or make obvious the cartilage repair implant recited in

new independent Claim 69. It is respectfully submitted that new Claim 69 is directed to patentable subject matter and is in condition for allowance.

Like new Claim 69, new Claim 84 recites a combination of a cartilage mixture and a decellularized allograft osteochondral plug. An annular space is formed when the osteochondral plug is placed in a bore formed in a defect area in a patient's articular cartilage. The annular space extends along substantially the entire length of the osteochondral plug. The cartilage mixture is positionable in the annular space, adjacent the osteochondral plug, in a quantity sufficient to promote tissue integration between the osteochondral plug and the patient's adjacent tissue. Applicants' attorney notes that unlike new Claim 69, new Claim 84 does not recite a product-by-process. Nevertheless, the combination recited in new Claim 84 includes the same structural features as new Claim 69, and is therefore believed to be patentable for the same reasons as new Claim 69.

In light of the above discussion of new independent Claim 69, applicants' attorneys respectfully submit that neither the Hart et al. Patent nor the secondary references, whether taken alone or in legitimate combination, disclose the combination recited in new independent Claim 84. In the foregoing circumstances, it is respectfully submitted that new Claim 84 is directed to patentable subject matter and is in condition for allowance for the same reasons that new Claim 69 is in condition for allowance.

Claims 47-68, which were rejected based on the same prior art grounds as independent Claim 44, now depend from new independent Claim 69. In such circumstances, Claims 47-68 are also believed to be in condition for allowance for the same reasons that amended independent Claim 69 is believed to be in condition for allowance.

New Claims 70-83 and 85-111 depend from new independent Claims 69 and 84, respectively. In such circumstances, Claims 70-83 and 85-111 are also believed to be in condition for allowance for the same reasons that new independent Claims 69 and 84 are believed to be in condition for allowance.

In view of the foregoing amendments and remarks, applicants' attorney respectfully requests the reconsideration and allowance of Claims 48-68 and the examination and allowance of new Claims 69-111. If such action cannot be taken, Examiner Singh is cordially invited to place a telephone call to applicants' attorneys in order that any outstanding issue may be resolved.

Applicants' attorneys note that the specification of the present application has been amended to make minor editorial revisions thereto. In addition, the term "phosphate buffered saline" and its acronym "PBS" were inserted in a paragraph of the "Background" section of the application that originally contained a similar term (i.e., phosphate saline buffer) to describe the same solution. Use of the acronym PBS for phosphate buffered saline is well known in the art (e.g., see Col. 5, Line 32 of U.S. Patent. No. 5,516,532, which was cited on the face of one of the patents discussed in the amended paragraph beginning on Page 7, Line 9 of the present application (U.S. Patent No. 6,437,018)). Currently amended Claim 56 and new Claim 93 recite the acronym PBS. The acronym PBS was also recited in originally-filed Claims 34, 38, 44. In such circumstances, applicants' attorneys respectfully submit that such amendment, and the other amendments of the specification, do not constitute new matter.

Applicants' attorneys note that as a result of the foregoing amendments, the present application contains 95 pending claims (i.e., Claims 11-46 and 48-111), including

six independent claims (Claims 13, 24, 34, 38, 69 and 84). In such circumstances, there are 34 new claims in excess of 20 (i.e., the number of claims permitted under the original filing fee) and one new independent claim in excess of three (i.e., the number of independent claims permitted under the original filing fee), for which extra claim fees of $1,988 (($52 x 34) + ($220 x 1)) are now due. The Commissioner is hereby authorized to charge such extra claim fees to Deposit Account No. 501561.

The accompanying Petition for a three-month extension of time authorizes the Examiner to charge the associated $1,110 extension fee to Deposit Account No. 501561. If there are any additional fees due as a result of this Amendment, including extension and petition fees, the Commissioner is hereby authorized to charge them to Deposit Account No. 501561.

Respectfully submitted,

GREENBERG TRAURIG, LLP

By: Ralph W. Selitto, Jr.
Reg. No. 26,996

GREENBERG TRAURIG, LLP
200 Park Avenue
P.O. Box 677
Florham Park, New Jersey 07932-0677
(973) 443-3550
selittor@gtlaw.com